Case Report

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NEXMIF Combined with *KIDINS220* Gene Mutation Caused Neurodevelopmental Disorder and Epilepsy: One Case Report

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Abstract

Summary of Medical History: A male infant, 8 months old, was admitted to hospital with cough and fever. The clinical symptoms were found to be mental retardation, obesity, dystonia, movement limitation, and visual retardation. Early development was normal, but after 6 months, the child developed upright head instability, difficulty grasping, and seizures.

Symptoms and Signs: The child presents with mental retardation, obesity, increased muscle tone, motor dysfunction, visual impairment, and seizures. Diagnosis: A whole exon test was performed to detect a neurite extension and migration factor (*NEXMIF*) gene mutation (NM_001008537.2: c.1042C > T (p. Arg348*)), which is known to be associated with intellectual disability and neurological symptoms. In addition, the test revealed a mutation in the Kinase D interacting substrate of 220 kDa (*KIDINS220*) gene (NM_020738.2: c.3242_3243insC (p. Leu1082AIafs*5)) with a heterozygous mutation in the father and wild type in the mother. Treatment: The patient was treated with anti-infection, aerosol inhalation, calcium supplement, and anti-epileptic drugs (levetiracetam), and the disease was controlled. Home and hospital rehabilitation is also underway.

Clinical Outcome: The condition of the child improved after treatment and no seizures occurred again. The patient needs continuous rehabilitation treatment and follow-up observation.

Conclusion: For male children with unexplained neurodevelopmental disorders and comorbidities such as obesity, dystonia, and seizures, mutations in related genes such as *NEXMIF* should be considered. Clinical practice should improve genetic testing as early as possible to provide a basis for genetic counseling.

Keywords

NEXMIF gene mutation; *KIDINS220* gene mutation; neurodevelopmental disorders; epilepsy

Introduction

Neurodevelopmental Disorders (NDD) is a group of diseases that affect the development of the central nervous system, widely affecting more than 3% of children worldwide [1,2]. This category of diseases involves hundreds of genes related to neurodevelopment which play important roles in key biological pathways such as neuronal migration, synaptic plasticity, gene expression, and protein synthesis [3]. In hereditary neurodevelopmental disorders, patients exhibit a range of symptoms, including dyskinesia, mental retardation, visual deficits, obesity, ventricular dilatation, and moderate developmental delay [4]. Some genetic mutations can cause neurodevelopmental disorders, including neurite extension and migration factor (*NEXMIF*) and Kinase D interacting substrate of 220 kDa (*KIDINS220*) genes [5]. Since 1981, researchers have constructed an almost complete atlas of genes on the X chromosome associated with intellectual disability (*XLID*), and more than 100 genes located on the X chromosome have been reported to be associated with *XLID* [6,7]. *NEXMIF* gene is a pathogenic gene of *XLID*, and patients with *NEXMIF* gene mutations not only have intellectual disabilities, but can also suffer from seizures, behavioral abnormalities, dystonia, and other neurological symptoms, as well as abnormalities of other systems. Homozygous mutations in the

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KIDINS220 gene can cause spontaneous abortion [8,9], and patients with heterozygous mutations also show intellectual disability and other neurological symptoms [10,11]. Based on a review of the literature, this case report discusses and analyzes the clinical phenotype and genotype characteristics of a male infant with *NEXMIF* gene combined with *KIDINS220* gene mutation, who was admitted to the Department of Pediatrics, Pu'er People's Hospital. This study was approved by the Ethics Committee of Pu'er People's Hospital (2024-003-01), and in accordance with the Declaration of Helsinki.

Clinical Report

The patient, a male infant, was born by caesarean section in the second day of the fourth fetus, he was born by cesarean section at 37 + 5 weeks, with a birth weight of 2.855 kg (–1 SD), a height of 48 cm (–1 SD ~ M), an unknown head circumference, and a normal APGAR (The first letter of Activity, Pulse, Grimace, Appearance, Respiration) score (1': 9, 5': 9). There was no intrauterine asphyxia or asphyxia at birth. The child had a history of prolonged jaundice (occurred on the third day after birth and lasted for a month before subsiding), was breastfed after birth, and had no feeding difficulties. No abnormalities were found during the pregnancy. Family history: The mother of the child was healthy, graduated from junior college, was employed at the local country hospital, and conceived naturally. During pregnancy, the mother did not catch a cold, was not exposed to radioactive substances, and did not have pregnancy-induced hypertension (PIH) syndrome or hyperglycemia. The father was healthy, graduated from university, and denied consanguineous marriage. The child has an elder sister, 4 years old, in good health. The family denied any history of similar illnesses. At 3 months after birth, it was found that the child would not raise his head and the limbs were less active. The child was admitted to the hospital for rehabilitation treatment due to developing head instability after 6 months. Cranial magnetic resonance imaging (MRI) was performed; the signal intensity in the bilateral occipital sulci was slightly enhanced in fluid attenuated inversion recovery, and it was recommended to review at intervals. Aged 8 months and 7 days, the child was hospitalized in our department due to bronchopneumonia. Physical examinations were as follows: body temperature was 37.2 °C, heart rate was 148 beats/min, respiratory rate was 34 breaths/min, body weight was 11 kg (above the 97th percentile), transcervical oxygen saturation was 96% (without oxygen inhalation). The child had poor facial and mental response, obesity, strabismus, absence of cyanosis in the lips, negative three-concave sign, coarse breath sounds in both lungs, audible coarse moist rales, and a slight wheezing. Cardiovascular and abdominal examinations revealed no abnormalities, and there was no edema present in the lower limbs. The child was poor at visual pursuit of small objects, and could be amused but did not vocalize laughter, engaged in less spontaneous activity, produced few voluntary vocalizations, and occasionally emitted "ee-l" sounds. The child tended to keep fists clenched, exhibited limited awareness of active grasp, but had adequate passive grasp ability. The supine position appeared symmetrical, but when pulled up from the supine position, the head tilted backward; In the prone position, the child could not maintain head elevation at 90° for a long time. The child could not sit unassisted, and had upright head instability. When assisted to stand, the support of the lower limbs was inadequate for weight-bearing, the muscle tone of the limbs was increased, and ankle clonus was negative.

During main auxiliary examinations in the hospital, abdominal ultrasound showed no abnormalities in the liver, gallbladder, spleen, pancreas, kidney, ureter, or bladder. Echocardiography showed that there was no abnormality in the structure and blood flow of the heart in the resting state. The results of pediatric TORCH [To (Toxopasma), R (Rubella.Virus), C (Cytomegalo.Virus), H (Herpes. Viru)] panel showed as follows: anti-Cytomegalovirus IgG: 15.859 AU/ML, anti-herpes simplex virus Type II antibody IgG: 16.949 AU/ML; all other parameters were within normal range. Human cytomegalovirus DNA quantification <400 copies/mL. Immunoglobin A was 0.09 g/L, immunoglobulin G was 3.43 g/L; immunoglobin M, complement 3, and complement 4 were normal. Epstein-barr (EB) virus antibody spectrum and EB virus DNA quantification showed no abnormalities. Infection markers were all negative and Chest Computed Tomography showed bronchopneumonia [12]. Video electroencephalogram (EEG) showed that there was no clear abnormality in electroencephalogram in early childhood. Urine genetic metabolism and blood genetic metabolism screening showed no abnormality, and 25-hydroxyvitamin D was 62 ng/mL.

During hospitalization, from July 17 to July 19, the child experienced one seizure each day, and the seizures manifested as unresponsiveness, binocular gaze, and limb twitching, lasting for several tens of seconds, and regaining consciousness after relief. After communicating with his family, an additional dose of Sodium valproate oral liquid [Sanofi (Hangzhou) Pharmaceutical Co., Ltd., Sinopod H20041435, 12 g:300 mL] was administered; the initial dose was 15 mg/(kg·d); dosed up incrementally; the dose was maintained at 20–30 mg/(kg·d) to control the attack and improve the whole exon detection.

Materials and Methods

5 mL peripheral blood from the subjects and parents was drawn from the subjects then extracted the Genomic DNA (gDNA) according to the manufacturer's standard procedure (MagPure Buffy Coat DNA Midi KF Kit, MAGEN). The gDNA was broken into 100–500 bp fragments by enzyme kit (Shearing Enzyme premix reagent, ENZYMATICS, Y9220L, Enzymatics, Beverly, MA, USA), then the 200–300 bp fragments were collected by magnetic bead (Vahtstm DNA Clean Beads, N411-01, VAZYME, Nanjing, China). And then built up single individual DNA library after Ligation-mediated polymerase chain reaction (LM-PCR) and purification. The library was enriched 16 h at 65 °C by array hybridization (HyperExome, 09062637001; ROCHE, Basel, Switzerland), finally, sequenced with PE100+10 on MGISEQ-2000 and data analysis. SOAPnuke (v1.6.5, Shenzhen BGI Co., Ltd., Shenzhen, China) [13] software was used to evaluate the sequencing quality of Raw reads. Reads with low quality and contaminated by joints were removed to obtain clean reads. Meanwhile, the sequence capture effect was evaluated. GATK (The Broad Institute, formerly the Broad Institute of MIT and Harvard, evolved from a decade of research collaborations among MIT and Harvard scientists.) [14] software (version 4.2.1.0, Broad Institute, Cambridge, MA, USA) was used to query single nucletide variant (SNV) and insertion and deletion (Indel) to generate the result of base polymorphism in the target region, and then multiple databases were compared to identify suspected mutations. We noted and filtered the BGI-Varanno self-developed algorithm. All pathogenic mutations were validated by Sanger method to validate the results of gene chip capture and high-throughput sequencing.

Results

Whole exome sequencing (WES) [15] indicated the following mutation in NEXMIF: NM_001008537.2: c.1042C > T (p. Arg348*), gene subregion EX3/CDS2. Genotype: the proband was hemizygous, and both parents were wild-type. According to The American College of Medical Genetics and Genomics (ACMG) variant classification guidelines, the mutation was rated as pathogenic (PVS1+PS2_M+PM2), as shown in Fig. 1. Secondary examination results indicated a mutation in KIDINS220: NM_020738.2: c.3242-3243insC (p. Leu1082AIafs*5), gene subregion EX24/CDS23. Genotype: the proband was heterozygous, the father was heterozygous, and the mother was wild-type. According to the ACMG variant classification guidelines, the mutation was rated as suspected pathogenic (PVS1+PM2), as shown in Fig. 2.

Discussion

Cantagrel *et al*. [16] first identified two novel genes that were disrupted by breakpoints: *KIAA2022* in Xq13.2 and *P2RY8* in Xp22.3, through identifying pericentric inversion of the X chromosome inv (X) (p22.3; q13.2) segregating in the XLID family. The study found no phenotypic consequences due to P2RY8 haploinsufficiency in carriers' mothers; female carriers are not affected, whereas male carriers have severe Mental retardation (MR) due to absence of the *KIAA2022* (also called *NEXMIF*) gene product. The *NEXMIF* gene is located at Xq13.2 and has a length of 192 kb, and its open reading frame contains 4 exons, encoding a protein with 1516 amino acids. NEXMIF is highly expressed in fetal brain, adult cerebral cortex, and cerebellum, and less expressed in heart, kidney, and lung. The extracellular matrix protein encoded by the *NEXMIF* gene plays an important role in the development of the nervous system, affecting the migration, localization, differentiation, and maturation of neurons. Gene mutation may lead to abnormal function of this protein, thereby affecting the formation of the extracellular matrix and subsequently affecting the normal development of neurons. Recently, a study was reported that *NEXMIF* mutations are associated with X-linked intellectual developmental disorder 98 (XLID98, OMME # 300912), which is a severe neurodevelopmental disorder syndrome characterized by delayed psychomotor development, poor language, behavioral abnormalities, or seizures [17]. The *NEXMIF* knockout mice show spontaneous seizures, autism-like behaviors, and intellectual disability [5]. KIDINS220 is a transmembrane protein universally expressed in the central nervous system (CNS) and peripheral nervous system (PNS), and is present in excitatory and inhibitory neurons as well as glial cells. At the subcellular level, it is present throughout the cell body, dendrites and axons, and in cytoplasmic domains involved in protein-protein interactions. The pre-synaptic brain-derived neurotrophic factor (BDNF) signaling pathway is involved in controlling neuronal activity, glutamate release, and post-synaptic Tyrosine Kinase receptor B (TPKB)-dependent retrograde signaling events associated with GABA release. The pathway includes multifunctional transmembrane proteins involved in nervous system development [18,19], and is a major determinant of neuronal and cardiovascular development. In a previous study, when *KIDINS220* was knocked out, the embryo died late in gestation and showed extensive cell death in the central and peripheral nervous systems. Primary neurons in mice exhibited reduced responsiveness to BDNF, and the embryo also showed marked cardiac abnormalities [20]. In addition, studies have shown that the conditional knockout of *KIDINS220* in the brain is characterized by

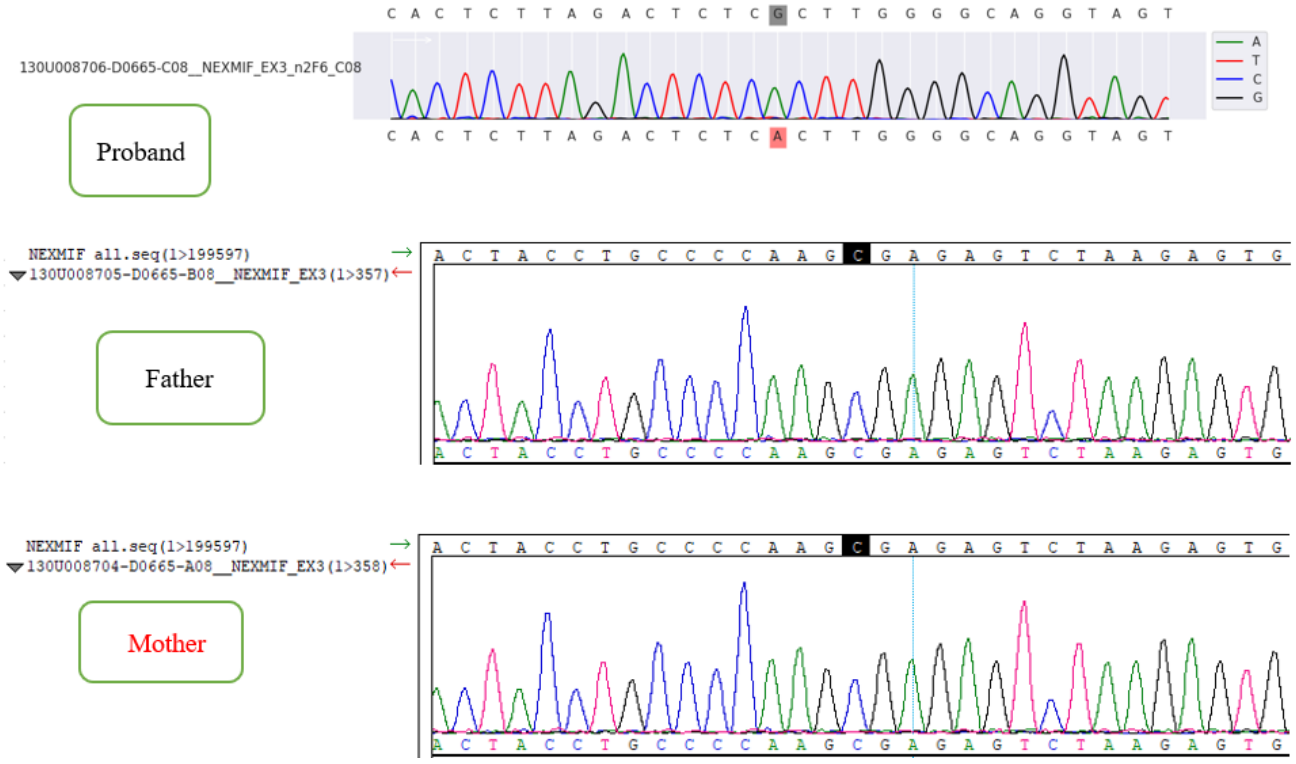

Fig. 1. NEXMIF: NM_001008537.2: c.1042C > T (p. Arg348*). NEXMIF, neurite extension and migration factor.

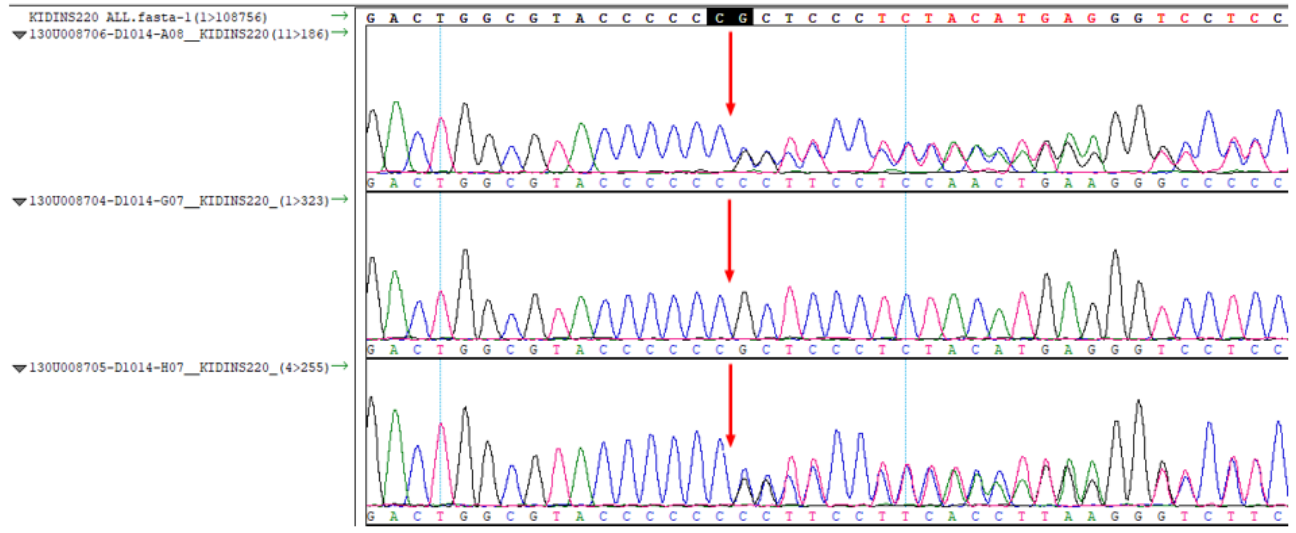

Fig. 2. KIDINS220: NM_020738.2: c.3242_3243insC (p. Leu1082Alafs*5). KIDINS220, Kinase D interacting substrate of 220 kDa; Remark: 130u008706 (proband), 130u008704 (mother), 130u008705 (father).

ventricular enlargement in the absence of cell death and a lack of dendritic dendrites in several cortical regions, leading to behavioral changes. Increasing evidence suggests that KIDINS220 mutation is linked to onset of severe neurodevelopmental disorders [21]. Homozygous *KIDINS220* gene mutation can lead to spontaneous abortion. However, in case reports, a heterozygous truncating variant in KIDINS220 was related to spastic paraplegia, intellectual disability, nystagmus, and obesity (SINO-OMIM 617296) [22,23], while the clinical symptoms of the child were relatively mild [24].

In this study, gene detection identified ① NEXMIF: NM_001008537.2: c.1042C > T (p. Arg348*) mutation, chromosome location: chrX:73963350, gene subregion EX3/CDS2, which is a nonsense variant; c.1042C > T leads to the substitution of the encoding amino acid arginine residue at 348 by the stop codon, the early termination of transcription and translation, resulting in the truncation of the corresponding protein product, which belongs to the lose-function variant, consistent with PVS1 evidence. This variant was not found in gnomAD, a normal control population database, which was consistent with PM2 evidence. The proband was hemizygous and both parents were wild-type, suggesting a new mutation, consistent with PS2_M evidence (PS2 was downgraded because the phenotype of the child was not highly specific), which was confirmed by subsequent Sanger sequencing (Fig. 1). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the mutation is rated as a pathogenic variant (PVS1+PS2_M+PM2).

② KIDINS220: NM_020738.2: c.3242_3243insC (p. Leu1082Alafs*5) mutation, chromosome location: chr2:8890413, gene subregion EX24/CDS23; this is a frameshift mutation, and c.3242_3243insC causes frameshift at 1082 bits of coding amino acid, resulting in changes in the reading frame and a series of downstream codon changes, which belongs to a los-function mutation and is consistent with PVS1 evidence. In the normal control population database gnomAD, the frequency of this mutation was very low, which was consistent with PM2 evidence. The proband was heterozygous, inherited from the father, and the mother had the wild type, which was confirmed by subsequent Sanger sequencing (Fig. 2). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the mutation is rated as a suspected pathogenic variant (PVS1+PM2) because it is inherited from a nonphenotypic father. The cases reported in autosomal dominant inheritance (AD) mode in Online Mendelian Inheritance in Man (OMIM) were mostly new mutations, and the presence of this gene was considered. There were reports of *KIDINS220* gene function loss, but it has also been reported [22] that in 5 unaffected individuals, there were three different truncated variants in the *KIDINS220* gene: E1530X, R1736X, and S1740X. These changes also occurred in the last exon of the gene, suggesting that not every loss-of-function variant leads to a phenotype. The clinical manifestations of the children were similar to those reported in *NEXMIF* gene mutation and/or *KIDINS220* gene mutation [22–24]. Thus, in the case of *NEXMIF* combined with *KIDINS220* gene mutation, we can speculate that there is a related pathway.

At present, Wechat video call follow-up is conducted every 3 months to understand the movement, language, behavior, and epilepsy control of the child. As of the latest follow-up before submission, the child has been administered sodium valproate oral solution for seizures, and has not had another seizure to date. Stamberger *et al*. [25] reported the use of valproic acid alone or in combination with levetiracetam, lamotrigine, and ethosuximide pairs Seizures caused by mutations in the *NEXMIF* gene were effective, but only 17.6 percent were the patient's epilepsy can be completely controlled. In other aspects of follow-up, the child could maintain head elevation and shout "mom" unconsciously, but could not sit steadily, did not step forward while holding the foot, and could not stand. Weight gain had slowed down, and the child often suffered from respiratory infections. Regular follow-up is helpful to better grasp the changes in the condition of children, improve the quality of life of patients, and relieve the tension and anxiety of parents. Although patients with *NEXMIF* gene mutations have diverse clinical manifestations, multiple system involvement, and severe phenotypes in some patients, there is no evidence that *NEXMIF* gene mutations seriously affect patient longevity. Patients with *NEXMIF* gene mutation often have a variety of systemic symptoms, and later may need multidisciplinary cooperation and active symptomatic treatment.

Conclusion

NEXMIF combined with *KIDINS220* gene mutations are rare in children. *NEXMIF* gene mutations should be considered in male children with unexplained intellectual disability, obesity, dystonia, and seizures. It is better to perform gene detection as soon as possible to provide a basis for identifying the cause and later rehabilitation treatment and genetic counseling.

Availability of Data and Materials

The data of this study are available from the corresponding author upon reasonable request.

Author Contributions

TTF and HLQ designed the research study. HLQ, DJP and YZ performed the research. YHZ provided the advice on the genetic testing. XZ analyzed the data. All authors contributed to the drafting or important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Pu'er People's Hospital (2024-003-01), and in accordance with the Declaration of Helsinki, and got the consent and support of parents.

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Conflict of Interest

The authors declare no conflict of interest.

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